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Language	English
Abstract	Purpose: Conflicting data have been reported regarding development of serum antibodies to botulinum A toxin. The purpose of this study is to determine conclusively whether antibody production to this toxin occurs in humans, and, if so, to determine its relationship, if

	any, to length of treatment, total cumulative dose, and clinical response to treatment. Methods: Sixty-five sera samples from 42 adults treated with botulinum A toxin for essential blepharospasm, hemifacial spasm, or spasmodic torticollis were analyzed via a sphere-linked immunodiagnostic assay for antibody production. Results were plotted against length of treatment, number of injections, cumulative dose, and treatment effect produced. Results: Twenty-four (57%) of the 42 patients produced antibodies in all three diagnostic groups. No significant differences were found between antibody producers and nonproducers with respect to age (P = 0.216), length of treatment (P = 0.586), number of injections (P = 0.619), or total cumulative dose (P = 0.286). Within the antibody-producing group, there was no significant correlation between amount of antibody and length of treatment (P = 0.081), number of injections (P = 0.134), or cumulative dose (P = 0.250). The presence of demonstrable antibodies in serum did not affect the clinical responsiveness to injection. Conclusion: Antibody production is present in a majority of patients treated with botulinum A toxin. The sphere-linked immunodiagnostic assay is a reliable and reproducible method for detecting and quantifying these antibodies. When antibody production occurs, it is likely due to variations in individual immune responsiveness and appears to have no direct effect on the patient's clinical response to treatment.
Major Concepts	Clinical Endocrinology: Human Medicine, Medical Sciences; Immune System: Chemical Coordination and Homeostasis; Metabolism; Muscular System: Movement and Support; Pathology; Pharmacology; Sense Organs: Sensory Reception; Toxicology
Biosystematic Codes	[07810] Endospore-forming Gram-Positives [86215] Hominidae
Super Taxa	[07810] Endospore-forming Gram-Positives, Eubacteria, Bacteria, Microorganisms [86215] Hominidae, Primates, Mammalia, Vertebrata, Chordata, Animalia
Taxa Notes	Endospore-forming Gram-Positives: Bacteria, Eubacteria, Microorganisms; Hominidae: Animals, Chordates, Humans, Mammals, Primates, Vertebrates
Organisms	endospore-forming gram-positive rods and cocci [Endospore-forming Gram-Positives]; human [Hominidae]
Miscellaneous Descriptors	BENIGN ESSENTIAL BLEPHAROSPASM; HEMIFACIAL SPASM; SPASMODIC TORTICOLLIS TREATMENT; SPHERE-LINKED IMMUNODIAGNOSTIC ASSAY; TOXICITY
Year of Publication	1993
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NEUROLOGY

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Response and immunoresistance to botulinum toxin injections

[Articles]

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Received November 8, 1994. Accepted in final form February 3, 1995.

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Abstract

Botulinum toxin antibodies (ABS) may be a reason why occasionally patients do not have a response to injections with botulinum toxin type A (BTX).We tested 86 patients with cervical or oromandibular dystonia for the presence of BTX ABS; 20 were positive and 66 were negative. All patients who tested positive had no response to BTX injections on at least two consecutive treatment sessions. When compared with 22 randomly selected patients with negative BTX ABS results, the patients with positive BTX ABS tests had an earlier age at onset (mean age: 31.8 plus minus 16.7 years versus 43.4 plus minus 10.5; p less than 0.05), higher mean dose per visit (249.2 plus minus 32.5 U versus 180.8 plus minus 68.7, p less than 0.0005), and higher total cumulative dose (mean dose: 1,709 plus minus 638 U versus 1,066 plus minus 938; p less than 0.01). Four out of five patients with positive ABS tests later had a response to botulinum toxin type F injections. Of 26 patients with negative BTX ABS results who were tested because of poor response on at least one visit, 21 had good response after subsequent injection and five had no effect. Except for young age at onset and higher dosages, there were no other factors that could reliably predict which patients would become immunoresistant to BTX type A injections. Treatment with alternate serotypes may offer clinical benefit to this group of patients. Absence of detectable BTX ABS may occur in patients with poor response to BTX injections because of inadequate dosage, injections of inappropriate muscles, or poor sensitivity of the BTX ABS bioassay.

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Injections of botulinum toxin type A (BTX) provide effective, symptomatic relief for several disorders characterized by abnormal muscular contractions, such as dystonia, spasticity, tremors, tics, and other motor disorders. [1] BTX injections are considered the treatment of choice for many of the focal dystonias, particularly blepharospasm, cervical dystonia (torticollis), laryngeal dystonia (spasmodic dysphonia), and task-specific dystonias (eg, writer's cramp). Although the benefits persist in the vast majority of patients after repeated injections, [2] in some patients the condition becomes unresponsive to subsequent treatments. [3,4] One reason for the development of resistance to BTX treatment is the development of blocking antibodies (ABS). In this study, we

sought to determine the causes of resistance and to identify risk factors for the formation of ABS.

Methods.

Eighty-six of 1,321 patients who received BTX injections on 6,549 visits at the Baylor College of Medicine Movement Disorder Clinic were tested for BTX ABS. Twenty-two were randomly selected for this study, which was approved by the Baylor Institutional Board for Human Research. The remainder were tested because of lack of or inadequate response to BTX injections (60 patients) or at the request of the patients (four patients), even though they had had a response to the treatment.

The response to treatment was rated on a 0 to 4 ``peak effect'' scale (0: no effect; 1: mild effect, no functional improvement; 2: moderate improvement, no change in functional disability; 3: moderate change in severity and function; and 4: marked improvement in severity and function). ``Lack of or inadequate response'' was defined as peak effect of 0 or 1. This study used the Allergan, Inc, preparation of BTX (BOTOX).

The presence of ABS was tested using a bioassay originally described by Hatheway et al [5,6] at the Center for Disease Control and performed by the Northview Pacific Laboratories, Berkeley, CA. Results of this qualitative bioassay are reported as either positive or negative. A positive result, indicating the presence of ABS in the patient's serum, occurs when the patient's serum neutralizes the effects of BTX and prevents the death of mice inoculated with the toxin. In a negative result, mice inoculated with BTX die, presumably because they are not protected by circulating ABS.

Results.

Of the 86 patients who were tested for BTX ABS, 20 had positive results and 66 had negative; 22 who had negative results were randomly tested. Five patients were tested more than once: in one, results turned negative 1 1/2 years after initial positive test results; in the remainder results were initially negative and subsequently became positive. These latter patients were included only in the ABS-positive group. All patients who had positive tests had no response to BTX (peak effect of 0 or 1 on at least two consecutive treatment sessions). All these patients were receiving BTX injections for cervical dystonia, except for one who had oromandibular dystonia manifested by forceful, spasmodic jaw closure. That patient's condition eventually failed to improve even with botulinum toxin type F. The other four patients treated with botulinum toxin type F obtained satisfactory but short-lasting improvement. None of the randomly tested patients had a positive BTX ABS test. This group was composed of 16 patients with cervical dystonia, five with cranial dystonia, and one with hand/arm dystonia.

Although there was a marked overlap between the two groups, the patients with positive BTX ABS results had an earlier age at onset (mean age: 31.8 plus minus 16.7 years versus 43.4 plus minus 10.5; p less than 0.05), higher mean dose per visit (249.2 plus minus 32.5 U versus 180.8 plus minus 68.7, p less than 0.0005), and higher total cumulative dose (mean dose: 1,709 plus

minus 638 U versus 1,066 plus minus 938; p less than 0.01) as compared with the randomly selected patient group Table 1. There was no statistical difference between patients with negative and positive BTX ABS results for any other variable, including gender, age, duration of symptoms, total visits, number of visits, inter-injection interval, and duration of treatment.

Clinical variables	+ Antibodies (range)	– Antibodies (range)
N	20	22
Reason for test	Poor response	Random selection
Gender (M/F)	5/15	10/12
Mean age (yr)	46.2 ± 13.5 (15-77)	50.4 ± 10.9 (30-75)
Mean age at onset (yr)	31.8 ± 16.7* (1-54)	43.4 ± 10.5* (24-59)
Mean duration of symptoms (mo)	172.6 ± 165.9 (15-552)	108.1 ± 155.5 (6-728)
Mean peak effect (immediately before testing)	0.78 ± 1.2‡ (0-3)	2.95 ± 1.46‡ (0-4)
Mean total cumulative dose (U)	1,709 ± 638* (500-3,000)	1,066 ± 938* (100-3,850)
Total number of visits	148	140
Average number of visits	7.3 ± 2.7 (2-12)	6.4 ± 5.6 (1-23)
Mean inter-injection interval (d)	125.5 ± 29.7 (72-181)	116.3 ± 56.6 (0-225)
Mean dose per visit (U)	249.2 ± 32.5† (189-310)	180.8 ± 68.7† (29-290)
Duration of treatment (yr)	2.53 ± 1.28 (0.5-5.0)	2.36 ± 2.23 (0-8.3)

* $p < 0.01$.
† $p < 0.0005$.
‡ $p < 0.00001$.

Table 1. Clinical correlates in patients tested for botulinum toxin antibodies

Of 26 patients tested because of poor response to at least one treatment session and who received additional injections, 21 had good response (peak effect more than equals 2) after subsequent injection and five had minimal or no effect (peak effect less than equals 1). Six patients were later treated surgically with cervical rhizotomy: two subsequently received BTX injections and had good responses, two had only slight improvement, and two were lost to follow-up.

Discussion.

This study shows a 100% correlation between the presence of BTX ABS, as determined by the mouse bioassay, and complete failure of response to BTX injections. The patients with positive ABS results had absolutely no response and no atrophy after BTX injections although all but one had had responses in the past. The one patient with oromandibular dystonia, who did not have an improvement even with dosages as high as 400 U per treatment visit, later also did not have a response to botulinum toxin type F. Our study also establishes a link among the mean dose per treatment session, total cumulative dose, and the development of BTX antibodies Table 1. Since we had always waited at least 1 month between injections, we did not observe the effects of ``boosters'' on ABS formation. There was no difference in the frequency of treatment sessions between our patients with and without ABS. This contrasted with another study [4] that showed a direct correlation between the presence of ABS and ``booster'' injections, usually administered within 2 to 3 weeks after the initial treatment. In that study, ABS were detected in 24 of 559 patients (4.3%), and 10.5% of the 559 were estimated to have developed resistance to BTX. Since the investigators did not indicate how many patients were actually tested, the frequency of ABS could not be determined from that study. [4] A sub-analysis of their results on patients with BTX resistance identified three potential risk factors for the development of BTX resistance: (1) frequent injections, (2) ``booster'' injections, and (3) high doses of BTX per treatment.

The frequency of BTX ABS has been reported to be in the 0 to 10% range, based on the results of the in vivo mouse bioassay. [3,4,6-8] In contrast, Siatkowski et al [9] reported positive ABS in 57% of 42 patients treated with BTX for blepharospasm, hemifacial spasm, and cervical dystonia. This Figure wasbased on a new test using a sphere-linked immunodiagnostic assay (SLIDA). Although this assay apparently has a four-fold greater sensitivity than ELISA, the presence of ABS detected by the SLIDA technique failed to correlate with the patient's clinical response. [9] Since the method fails to detect neutralizing ABS and the nature of the ABS is unknown, the SLIDA method has limited value in assessing lack of clinical response to BTX treatment. ELISA has been used for the detection of BTX ABS, but clinical correlation between the presence of such ABS and a lack of response to BTX injections has not been established. [6,10,11] In one study, [12] only three of 96 patients with focal dystonia who received repeated injections of the preparation (Porton Down, UK) had ABS detected by an in vivo toxin neutralization test. The inter-injection interval was shorter in the patients with positive ABS tests, but there was no correlation with dosage or with clinical response. Again, the assay apparently did not detect blocking, clinically relevant ABS. In addition to lack of atrophy of the muscles that underwent injection, other physical examination techniques can be used to detect BTX resistance. For example, the lack of depression of transverse lines in the forehead after a unilateral injection of 10 to 15 U of BTX in the frontalis muscle, a site remote from that of the therapeutic injection, has

been suggested as evidence for BTX resistance. [13] The validity of this observation, however, has not yet been tested. We are currently evaluating the effects of unilateral injection into the corrugator muscle. In patients who are responsive to BTX, such injection produces asymmetrical contraction, whereas in immunoresistant patients the symmetry of eyebrow contractions is preserved.

We believe that the chief reasons for the marked differences in the frequencies of ABS are: (1) heterogeneous patient population with various conditions requiring different dosages of BTX and (2) utilization of different techniques for detecting ABS. ABS can be directed against different components of the BTX preparation; while some are directed against the BTX molecule, others are directed against the associated proteins. Only those ABS that effectively block the biologic activity of the toxin are clinically relevant. Although cumbersome and expensive, the mouse neutralization bioassay is currently considered the most reliable assay for biologically relevant immunoresistance. [6] None of our patients with positive ABS results, measured by the mouse bioassay, had responses to subsequent BTX injections. In some of those with no response, however, the mouse bioassay failed to detect BTX ABS. This may indicate lack of sensitivity of the assay or other reasons for poor response, such as selection of wrong muscles or inadequate dose.

Patients who develop ABS to BTX type A, and thus become resistant to this type of toxin, usually experience benefits with other types of toxins, such as botulinum toxins B and F. [14-17] Although the magnitude of improvement with these toxins is similar to that with type A, the duration of the benefit tends to be shorter. Ten of 15 torticollis patients [17] who became resistant to BTX A improved with botulinum toxin F, but the benefits lasted only 1 month rather than the 3 months of benefits experienced before they became resistant to BTX type A. While the duration of benefit from botulinum toxin type B appears longer than from type F, only long-term studies will determine whether the alternative types of botulinum toxin offer any advantages other than their clinical benefits in patients who become immunoresistant to BTX type A. Alternating type A with one of the other types of botulinum toxin might reduce the long-term risk of immunoresistance.

In summary, BTX ABS formation is one explanation for the occasional lack of response to BTX injections. Treatment with alternate serotypes may offer clinical benefit to this group of patients. Absence of detectable BTX ABS may occur in patients with poor response to BTX injections because of inadequate dosage or selection of inappropriate muscles; this condition warrants reinjection at higher dosages or at alternative sites.

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Accession Number: 00006114-199509000-00019

1: Neurology. 1998 Jun;50(6):1624-9.

Links

Mouse bioassay versus Western blot assay for botulinum toxin antibodies: correlation with clinical response.

Hanna PA, **Jankovic J**.

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OBJECTIVE: To compare the mouse protection bioassay (MPB) to the Western blot assay (WBA) in detecting antibodies against botulinum toxin A (BTX-A) and to correlate the assay results with clinical responses to BTX-A injections. METHODS: MPB and WBA assay results were compared in 51 patients (34 nonresponders and 17 responders) who received BTX-A injections, most commonly for cervical dystonia. A subset of patients received a "test" injection into either the right eyebrow (14) or right frontalis (12). RESULTS: Twelve patients with antibodies against BTX-A (Ab+) detected by WBA did not demonstrate antibodies (Ab-) by MPB. Conversely, five patients were Ab+ by MPB but Ab- by WBA. Specificity of the MPB was 100% on all three parameters (clinical, eyebrow, and frontalis injections), whereas WBA specificity was only 71% for clinical response but 100% for both eyebrow and frontalis responses. Sensitivities for both assays were low (33 to 53%). Of the 16 patients previously Ab+ by MPB, seven became negative on retesting after a mean interval of 33 months (range, 6 to 93 months). CONCLUSIONS: The lower specificity of the WBA compared to the MPB suggests that the WBA detects nonblocking antibodies. Eyebrow and frontalis "test" injections correlated well with MPB and WBA results and with clinical responses and may be useful in the evaluation of BTX nonresponders.

PMID: 9633703 [PubMed - indexed for MEDLINE]

1: Neurology. 1999 Oct 22;53(7):1431-8.

Full Text Neurology Links

Safety and efficacy of NeuroBloc (botulinum toxin type B) in type A-resistant cervical dystonia.

Brin MF, Lew MF, Adler CH, Comella CL, Factor SA, Jankovic J, O'Brien C, Murray JJ, Wallace JD, Willmer-Hulme A, Koller M.

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OBJECTIVE: To determine the safety and efficacy of botulinum toxin type B (BoNT/B) in patients with type A-resistant cervical dystonia (CD). Background: Local intramuscular injections of BoNT are an effective therapy for CD. After repeated use, some patients become resistant to therapy. BoNT/B, effective in type A toxin-responsive patients, is proposed as an alternative therapy for type A-resistant patients. METHODS: The authors performed a 16-week, double-blind, placebo-controlled trial of BoNT/B in type A-resistant patients with CD. After resistance to therapy was confirmed with the frontalis-type A test, placebo or 10,000 U BoNT/B was administered in a single session into two to four clinically involved muscles. The Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) was the primary efficacy measurement. TWSTRS-Total, three visual analog scales (Patient Global Assessment of Change, Principal Investigator Global Assessment of Change, Patient Analog Pain Assessment), and adverse events were assessed at baseline and weeks 2, 4, 8, 12, and 16. RESULTS: A total of 77 patients participated (38 placebo, 39 active). Improvements in severity, disability, and pain were documented in the BoNT/B-treated group. TWSTRS-Total scores were improved in the BoNT/B-treated group at weeks 4 ($p = 0.0001$), 8 ($p = 0.0002$), and 12 ($p = 0.0129$). All three visual analog scales demonstrated improvements at week 4 ($p < 0.0001$, 0.0001, and 0.001). A Kaplan-Meier analysis supported a duration of effect of 12 to 16 weeks in the active group. Dry mouth and dysphagia were self-limited adverse effects, reported more commonly in the BoNT/B group. CONCLUSIONS: Botulinum toxin type B (BoNT/B) (NeuroBloc) is safe and efficacious for the management of patients with type A-resistant cervical dystonia with an estimated duration of treatment effect of 12 to 16 weeks.

PMID: 10534247 [PubMed - indexed for MEDLINE]

1: Mov Disord. 1997 Sep;12(5):772-5.

Links

BotB (botulinum toxin type B): evaluation of safety and tolerability in botulinum toxin type A-resistant cervical dystonia patients (preliminary study).

Truong DD, **Cullis PA**, **O'Brien CF**, **Koller M**, **Villegas TP**, **Wallace JD**.

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Botulinum toxin (BTX) injection is considered the treatment of choice for patients with cervical dystonia (torticollis). We conducted a pilot, open-label, dose-escalation study with BTX type B in 12 patients who no longer responded clinically to injections with BTX type A. At the doses tested, BTX type B was safe and well tolerated without evidence of dose-limiting toxicity in this patient population. Mild-to-moderate adverse events generally resolved quickly and included asthenia, pain, nausea, dysphagia, hypertonia, and tremor. No serious adverse events or antibodies to type-B treatment were reported. Low-dosing-session (100-899 units) and high-dosing-session (900-1,500 units) groups were defined based on units administered per dosing session. Toronto Western Spasmodic Torticollis Rating Scale-Severity Scale (TWSTRS-Severity), Patient Analogue Pain Scale, and Physician and Patient Global Assessment Scales were measured during this study. The TWSTRS-Severity mean maximum percent improvement from baseline demonstrated a 9.9% versus 28.8% difference between the low-dose and high-dose groups, respectively. EFfectiveness was noted for the high-dose group on the Patient Analogue Pain Scale but not on the Global Assessment Scales.

PMID: 9380065 [PubMed - indexed for MEDLINE]

1: Mov Disord. 1998 Jan;13(1):150-4.

Links

Variability of the immunologic and clinical response in dystonic patients immunoresistant to botulinum toxin injections.

Sankhla C, Jankovic J, Duane D.

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Immunoresistance (Ab+) to botulinum toxin type A (BTX-A) has been a serious concern since the introduction of BTX-A in the treatment of dystonia and other disorders associated with abnormal muscle contractions. We studied seven patients who developed Ab+ and later reverted to antibody-negative (Ab-) status. These seven patients, six women (mean age, 56 years; range, 41-80 years), with an average duration of dystonia for all patients of 197 months (range, 84-360 months), received a total mean cumulative dose of 1659 units (U) (range, 810-1975 U), with an average dose of 207 U per visit. All of these patients became unresponsive to BTX-A treatment and became Ab+ as determined by mouse bioassay. Their response to BTX-A after they reverted to Ab- was analyzed. The average latency between the initial BTX-A treatment and development of Ab+ was 27 months (range, 1543 months). The average duration between the detection of Ab+ status and subsequent reversal to Ab- status was 30 months (range, 10-78 months). Six of these Ab- patients were reinjected with BTX-A, and all six benefited from repeat injections comparable with their earlier response. Three patients lost their clinical response to subsequent injections and were found to be again Ab+. Two of the five patients who became immunoresistant to BTX-A received botulinum toxin type F (BTX-F) injections and one patient received a single session of BTX-B with improvement in their symptoms. In conclusion, this unique group of patients who were Ab+ and became Ab- responded favorably to repeat BTX-A injections, but some lost the benefit with subsequent injections. These observations suggest that the anamnestic immunologic response to BTX-A can wane, but can be reactivated by repeat BTX-A treatments. The presence of antibodies did not interfere with the response to BTX-F or BTX-B injections, thus confirming the antigenic specificity of various BTX serotypes.

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: Neurology. 1995 Sep;45(9):1743-6. Links

Response and immunoresistance to botulinum toxin injections.

Jankovic J, **Schwartz K**.

Department of Neurology, Baylor College of Medicine, Houston, TX 77030, USA.

Botulinum toxin antibodies (ABS) may be a reason why occasionally patients do not have a response to injections with botulinum toxin type A (BTX). We tested 86 patients with cervical or oromandibular dystonia for the presence of BTX ABS; 20 were positive and 66 were negative. All patients who tested positive had no response to BTX injections on at least two consecutive treatment sessions. When compared with 22 randomly selected patients with negative BTX ABS results, the patients with positive BTX ABS tests had an earlier age at onset (mean age: 31.8 +/- 16.7 years versus 43.4 +/- 10.5; $p < 0.05$), higher mean dose per visit (249.2 +/- 32.5 U versus 180.8 +/- 68.7, $p < 0.0005$), and higher total cumulative dose (mean dose: 1,709 +/- 638 U versus 1,066 +/- 938; $p < 0.01$). Four out of five patients with positive ABS tests later had a response to botulinum toxin type F injections. Of 26 patients with negative BTX ABS results who were tested because of poor response on at least one visit, 21 had good response after subsequent injection and five had no effect. Except for young age at onset and higher dosages, there were no other factors that could reliably predict which patients would become immunoresistant to BTX type A injections. Treatment with alternate serotypes may offer clinical benefit to this group of patients. Absence of detectable BTX ABS may occur in patients with poor response to BTX injections because of inadequate dosage, injections of inappropriate muscles, or poor sensitivity of the BTX ABS bioassay.

PMID: 7675238 [PubMed - indexed for MEDLINE]

NiceZyme View of ENZYME: EC 3.4.24.69

Official Name	
Bontoxilysin.	
Alternative Name(s)	
Botulinum neurotoxin.	
Reaction catalysed	
Limited hydrolysis of proteins of the neuroexocytosis apparatus, synaptobrevins, SNAP25 or syntaxin. No detected action on small molecule substrates	
Cofactor(s)	
Zinc.	
Comment(s)	
Belongs to peptidase family M27.	
Cross-references	
PROSITE	PDOC00129
BRENDA	3.4.24.69
PUMA2	3.4.24.69
PRIAM enzyme-specific profiles	3.4.24.69
KEGG Ligand Database for Enzyme Nomenclature	3.4.24.69
IUBMB Enzyme Nomenclature	3.4.24.69
IntEnz	3.4.24.69
MEDLINE	Find literature relating to 3.4.24.69
MetaCyc	3.4.24.69
UniProtKB/Swiss-Prot	P10845, BXA1_CLOBO; Q45894, BXA2_CLOBO; P10844, BXB_CLOBO; P18640, BXC1_CLOBO; P19321, BXD_CLOBO; Q00496, BXE_CLOBO; P30995, BXE_CLOBU; P30996, BXF_CLOBO; Q60393, BXG_CLOBO;

View entry in original ENZYME format
View entry in raw text format (no links)

All UniProtKB/Swiss-Prot entries referenced in this entry, with possibility to download in

	Botulinum neurotoxin type B [Precursor]
Synonyms	**EC 3.4.24.69** **BoNT/B** **Bontoxilysin-B**
Contains	**Botulinum neurotoxin B light chain** **Botulinum neurotoxin B heavy chain**
Gene name	**Name: botB**
From	Clostridium botulinum [TaxID: 1491

==========

Welcome to the SIB BLAST Network Service

If results of this search are reported or published, please mention t
the computation was performed at the SIB using the BLAST network ser
The SIB BLAST network service uses a server developed at SIB and the
BLAST 2 software.

In case of problems, please read the online BLAST help.
If your question is not covered, please contact <helpdesk@expasy.org>

NCBI BLAST program reference [PMID:9254694]:
Altschul S.F., Madden T.L., Schäffer A.A., Zhang J., Zhang Z., Mille
Lipman D.J. Gapped BLAST and PSI-BLAST: a new generation of protein
database search programs. Nucleic Acids Res. 25:3389-3402(1997).

==========

Query: 19 AA
Date run: 2006-10-27 16:06:52 UTC+0100 on blast01.vital-it.ch
Program: NCBI BLASTP 2.2.13 [Nov-27-2005]
Database: UniProtKB
3,549,164 sequences; 1,165,290,707 total letters
UniProt Knowledgebase Release 8.9 consists of:
UniProtKB/Swiss-Prot Release 50.9 of 17-Oct-2006: 235673 entries
UniProtKB/TrEMBL Release 33.9 of 17-Oct-2006: 3297108 entries

Taxonomic view | NiceBlast view | Printable view

List of potentially matching sequences

Send selected sequences to
Clustal W (multiple alignment) Submit Query
Select up to...

☐ Include query sequence

Db AC Description

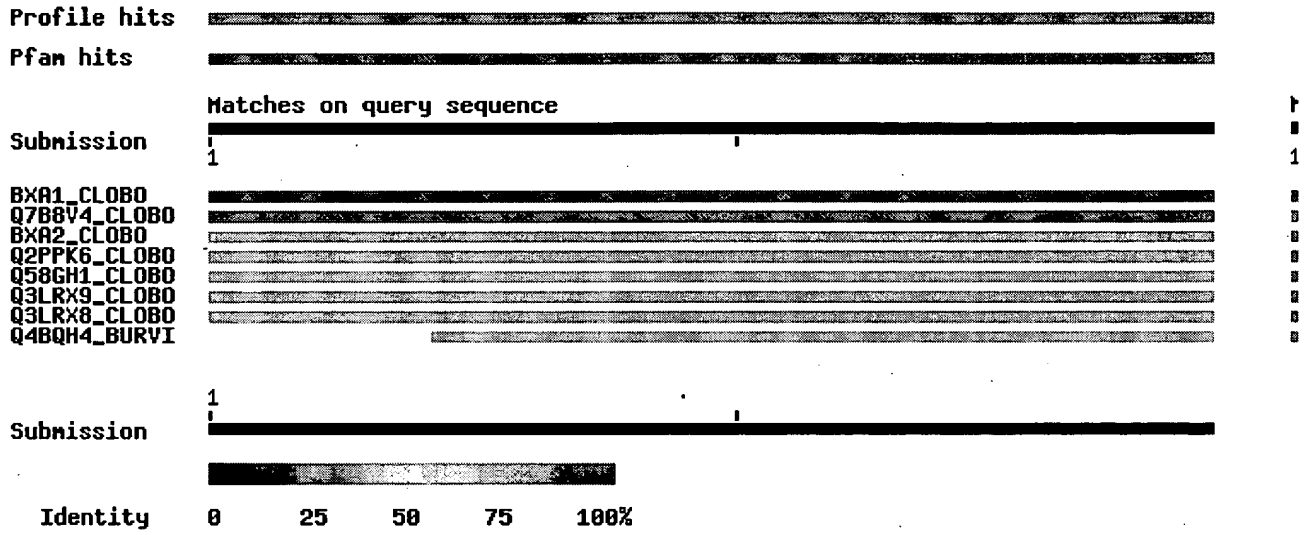
☐ sp P10845 BXA1_CLOBO Botulinum neurotoxin type A precursor (EC 3.
☐ tr Q7B8V4 _CLOBO BoNT/A (Neurotoxin BoNT) [bont/a] [Clostridium b

- ☐ sp Q45894 BXA2_CLOBO Botulinum neurotoxin type A precursor (EC 3.
- ☐ tr Q2PPK6 _CLOBO Botulinum neurotoxin type A [boNT/A] [Clostridiu
- ☐ tr Q58GH1 _CLOBO Type A2 botulinum neurotoxin [Clostridium botuli
- ☐ tr Q3LRX9 _CLOBO Neurotoxin type A [Clostridium botulinum]
- ☐ tr Q3LRX8 _CLOBO Neurotoxin type A [Clostridium botulinum]
- ☐ tr Q4BQH4 _BURVI MscS Mechanosensitive ion channel precursor [Bce

Graphical overview of the alignments

Click here to resubmit your query after masking regions matching PROSITE profiles or Pfam HMMs

(? Help) (use ScanProsite for more details about PROSITE matches)



Alignments

sp P10845 BXA1_CLOBO **Botulinum neurotoxin type A precursor (EC 3.4.24.69) (BoNT/A) (Bontoxilysin-A) (BOTOX) [Contains: Botulinum neurotoxin A light-chain; Botulinum neurotoxin A heavy-chain] [botA] [Clostridium botulinum]** 1295 AA align

Score = 63.0 bits (141), Expect = 1e-09
Identities = 19/19 (100%), Positives = 19/19 (100%)

```
Query: 1   IPYGVKRLEDFDASLKDAL 19
           IPYGVKRLEDFDASLKDAL
Sbjct: 800 IPYGVKRLEDFDASLKDAL 818
```

tr Q7B8V4 Q7B8V4_CLOBO **BoNT/A (Neurotoxin BoNT) [bont/a] [Clostridium botulinum]** 1296 AA align

Score = 63.0 bits (141), Expect = 1e-09
Identities = 19/19 (100%), Positives = 19/19 (100%)

```
Query: 1   IPYGVKRLEDFDASLKDAL 19
           IPYGVKRLEDFDASLKDAL
Sbjct: 801 IPYGVKRLEDFDASLKDAL 819
```

sp Q45894 BXA2_CLOBO **Botulinum neurotoxin type A precursor (EC 3.4.24.69) (BoNT/A) (Bontoxilysin-A) (BOTOX) [Contains: Botulinum neurotoxin A light-chain; Botulinum neurotoxin A heavy-chain] [botA] [Clostridium botulinum]** 1295 AA align

Score = 44.3 bits (97), Expect = 5e-04
Identities = 14/19 (73%), Positives = 14/19 (73%)

```
Query: 1   IPYGVKRLEDFDASLKDAL 19
           IPY VKRL DFDAS  D L
Sbjct: 800 IPYAVKRLKDFDASVRDVL 818
```

tr Q2PPK6 Q2PPK6_CLOBO **Botulinum neurotoxin type A [boNT/A] [Clostridium botulinum]** 1296 AA align

Score = 44.3 bits (97), Expect = 5e-04
Identities = 14/19 (73%), Positives = 14/19 (73%)

```
Query: 1   IPYGVKRLEDFDASLKDAL 19
           IPY VKRL DFDAS  D L
Sbjct: 801 IPYAVKRLKDFDASVRDVL 819
```

tr Q58GH1 Q58GH1_CLOBO **Type A2 botulinum neurotoxin [Clostridium botulinum]** 1296 AA align

Score = 44.3 bits (97), Expect = 5e-04
Identities = 14/19 (73%), Positives = 14/19 (73%)

```
Query: 1   IPYGVKRLEDFDASLKDAL 19
```

```
           IPY VKRL DFDAS  D L
Sbjct: 801 IPYAVKRLKDFDASVRDVL 819
```

tr Q3LRX9 Q3LRX9_CLOBO **Neurotoxin type A [Clostridium botulinum]** 1292 AA align

```
 Score = 44.3 bits (97), Expect = 5e-04
 Identities = 14/19 (73%), Positives = 14/19 (73%)

Query: 1   IPYGVKRLEDFDASLKDAL 19
           IPY VKRL DFDAS  D L
Sbjct: 797 IPYAVKRLKDFDASVRDVL 815
```

tr Q3LRX8 Q3LRX8_CLOBO **Neurotoxin type A [Clostridium botulinum]** 1296 AA align

```
 Score = 44.3 bits (97), Expect = 5e-04
 Identities = 14/19 (73%), Positives = 14/19 (73%)

Query: 1   IPYGVKRLEDFDASLKDAL 19
           IPY VKRL DFDAS  D L
Sbjct: 801 IPYAVKRLKDFDASVRDVL 819
```

tr Q4BQH4 Q4BQH4_BURVI **MscS Mechanosensitive ion channel precursor [Bcep1808DRAFT_6541] [Burkholderia vietnamiensis G4]** 832 AA align

```
 Score = 30.3 bits (64), Expect = 8.4
 Identities = 10/15 (66%), Positives = 11/15 (73%)

Query: 5   VKRLEDFDASLKDAL 19
           VKRL+ FDA L D L
Sbjct: 215 VKRLDAFDAELRDML 229
```

```
Database: UniProtKB
    Posted date:  Oct 17, 2006  4:29 PM
  Number of letters in database: 997,003,393
  Number of sequences in database:  2,996,474
```

```
  Database: /home/local/blastnet/database/EXPASY////UniProtKB.01
    Posted date:  Oct 17, 2006  4:36 PM
  Number of letters in database: 168,287,314
  Number of sequences in database:  552,690

Lambda     K      H
   0.334    0.294     1.69

Gapped
Lambda     K      H
   0.294    0.110    0.610


Matrix: PAM30
Gap Penalties: Existence: 9, Extension: 1
Number of Hits to DB: 12,299,442
Number of Sequences: 3549164
Number of extensions: 40613
Number of successful extensions: 3045
Number of sequences better than 10.0: 8
Number of HSP's better than 10.0 without gapping: 8
Number of HSP's successfully gapped in prelim test: 0
Number of HSP's that attempted gapping in prelim test: 3037
Number of HSP's gapped (non-prelim): 8
length of query: 19
length of database: 1,165,290,707
effective HSP length: 9
effective length of query: 10
effective length of database: 1,133,348,231
effective search space: 11333482310
effective search space used: 11333482310
T: 16
A: 15
X1: 15 ( 7.2 bits)
X2: 35 (14.8 bits)
X3: 58 (24.6 bits)
S1: 41 (21.5 bits)
S2: 64 (30.3 bits)
Wallclock time: 3 seconds
```

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UniProtKB/Swiss-Prot family/domain classification: peptidase M27 family

Family/domain

peptidase M27 family

Hierarchical classification

- all families and domains
  - family
    - **peptidase M27 family**

CC SIMILARITY line

This is the list of all UniProtKB/Swiss-Prot entries containing the line:

```
CC -!- SIMILARITY: Belongs to the peptidase M27 family.
```

extracted from the index of CC SIMILARITY lines.

UniProtKB/Swiss-Prot entries

Send selected sequences to Retrieve sequences (FASTA format)

Submit Query Select all

☐ BXA1_CLOBO (P10845),	☐ BXA2_CLOBO (Q45894),	☐ BXB_CLOBO (
☐ BXC1_CLOBO (P18640),	☐ BXD_CLOBO (P19321),	☐ BXE_CLOBO (
☐ BXE_CLOBU (P30995),	☐ BXF_CLOBO (P30996),	☐ BXG_CLOBO (
☐ TETX_CLOTE (P04958)		